

UNCLASSIFIED

AD 434424

DEFENSE DOCUMENTATION CENTER

FOR

SCIENTIFIC AND TECHNICAL INFORMATION

CAMERON STATION, ALEXANDRIA, VIRGINIA



UNCLASSIFIED

NOTICE: When government or other drawings, specifications or other data are used for any purpose other than in connection with a definitely related government procurement operation, the U. S. Government thereby incurs no responsibility, nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.

64-11

SAM-TDR-64-6

4 3 4 4 2 4

CATALOGED BY DDC  
AS AD No.

4 3 4 4 2 4

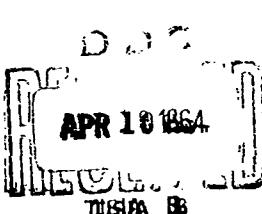
# ENDOCRINE AND METABOLIC EFFECTS OF SHORT-DURATION HYPEROXIA

TECHNICAL DOCUMENTARY REPORT NO. SAM-TDR-64-6

February 1964

USAF School of Aerospace Medicine  
Aerospace Medical Division (AFSC)  
Brooks Air Force Base, Texas

Task No. 775801



Qualified requesters may obtain copies of this report from DDC. Orders will be expedited if placed through the librarian or other person designated to request documents from DDC.

When U. S. Government drawings, specifications, or other data are used for any purpose other than a definitely related government procurement operation, the government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

## **FOREWORD**

This report was prepared by the following personnel in the Physiology Department:

**HENRY B. HALE, Ph.D.**  
**EDGAR W. WILLIAMS, B.A.**  
**JOHN E. ANDERSON, M.A.**  
**JAMES P. ELLIS, JR., M.A.**

Statistical analyses were performed by Richard C. McNee, Biometrics Department.

## ABSTRACT

This investigation was concerned with the effects of breathing 100% oxygen (by mask) at 1 atmosphere ambient pressure for 4 hours on sympathoadrenal, adrenocortical, and metabolic functions in healthy human subjects. Control determinations were made on the same subjects on a separate occasion by having the subjects breathe room air (by mask). Sympathoadrenal activity was appraised by means of urinary epinephrine and norepinephrine determinations; adrenocortical activity was appraised by means of plasma cortisol and urinary 17-hydroxycorticosteroid determinations; and metabolic appraisal was made by means of urinary creatinine, urea, uric acid, phosphate, potassium, and sodium. Evidence of hyperoxia-induced adrenocortical and sympathoadrenal depression was found—plasma cortisol concentration, as well as catecholamine excretion, falling below the control levels. Urine volume also was relatively low, as were urinary sodium and phosphate values. Mask discomfort was shown to be an obscuring factor, since it acted oppositely to hyperoxia in many respects.

This technical documentary report has been reviewed and is approved.



ROBERT B. PAYNE  
Colonel, USAF, MSC  
Chief, Operations Division

## **ENDOCRINE AND METABOLIC EFFECTS OF SHORT-DURATION HYPEROXIA**

### **1. INTRODUCTION**

Additional knowledge of the physiology of hyperoxia is needed in view of the frequent use of 100% oxygen by flying personnel and astronauts during preflight periods and by research and training personnel prior to decompression in altitude chambers. The possibility that preflight hyperoxia may be a predisposing factor for subsequent stresses seems not to have been investigated extensively, nor is there much knowledge on the compensatory responses to high oxygen pressure. Sympathetic and neuroendocrine changes during hyperoxia seem likely since a parasympathetic response to hyperoxia has been demonstrated in the human (3). Logically, sympathoadrenal and adrenocortical depression would be beneficial in hyperoxia, since it is known that epinephrine and corticosteroids have enhancing effects on oxygen toxicity (11). The present investigation, which was preliminary in nature, deals with sympathoadrenal and adrenocortical responses to hyperoxia in healthy human subjects. In addition, certain metabolic functions were examined for evidence of oxygen-sensitivity.

### **2. METHODS**

A group of 24 healthy adult men was studied on two occasions, with the time between tests amounting to more than a week. On both occasions, the subjects rested in reclining chairs from 0800 to 1200 hours, wearing aviator-type oxygen masks which were strapped tightly to the face and connected to diluter-demand oxygen regulators which delivered either pure oxygen (the experimental situation) or room air (control situation). The mask contains a single flapper valve which permits the expired air to be blown off to the outside atmosphere. During inspiration, the flapper seals tightly

against the valve seat, and no ambient air can be admitted to the mask through this channel. The regulator is a simple mechanism operated by normal changes in pressure occurring during the breathing cycle. Thermal comfort was insured by having air temperature in the test chamber constant at 75° F. Barometric pressure approximated 750 mm. Hg. To offset pre-existing variation in metabolic status in the subjects at the different test times, half of the subjects breathed oxygen on the first occasion and room air on the second, while the remaining subjects were tested in the opposite order. Television programs were viewed by the subjects during both tests.

Venous blood samples taken terminally were analyzed for cortisol, using the method of Sweat (14), which relies on sulfuric acid-induced fluorescence. Preliminary (pretest) cortisol determinations, although highly desirable, were not made because it was thought that venipuncture at this particular time might have an obscuring influence on physiologic responses to hyperoxia.

Urine samples taken terminally were analyzed for 17-hydroxycorticosteroids (17-OHCS) by means of the Reddy method (13), which is based on the phenylhydrazine reaction. These determinations, along with plasma cortisol, provide means for assessing adrenocortical activity.

Urinary epinephrine and norepinephrine determinations were made by means of a modification of the trihydroxyindole method (4). Epinephrine excretion relates to adrenomedullary activity primarily, while norepinephrine reflects changes in sympathetic nerves (15). The Technicon AutoAnalyzer was used to measure urinary creatinine, urea, uric acid, inorganic phosphate, potassium, and sodium.

These latter urinary constituents reflect changes in nitrogen and mineral metabolism, as well as changes in acid-base balance.

### 3. RESULTS

Evidence of slight adrenocortical depression was found—cortisol values for hyperoxia and normoxia averaging, respectively, 6.2 and 7.8  $\mu\text{g}/100 \text{ ml. plasma}$  ( $P < .025$ ). The value obtained during normoxia is not statistically different from one obtained previously (9) for nonstressed adult males (8.2  $\mu\text{g}/100 \text{ ml. plasma}$ ); the value obtained during hyperoxia, however, is significantly below this level ( $P < .005$ ).

A strict time schedule was followed to have the normoxia and hyperoxia tests agree precisely with respect to time of day. Since plasma cortisol concentration normally falls progressively throughout the morning hours (1, 10), nonadherence to a strict time schedule would have made interpretation impossible. The slightly lower cortisol value found after 4 hours of oxygen breathing, therefore, can be considered physiologically meaningful, and oxygen influence on the processes that underlie or control the diurnal shift may be inferred. Since oxygen effects (at 1 atmosphere) are known to be slow in onset, generally not appearing in the first 4 hours (11), it is not surprising to find this effect to be low in magnitude.

In processing the urine samples, it was necessary to store them temporarily in a freezer. Unfortunately, electrical power failure occurred which caused thawing of some of the urine samples; consequently, the urinary 17-OHCS data were incomplete. Based on the data for only 12 of the 24 subjects, urinary 17-OHCS excretion during normoxia agreed with that found previously for nonstressed men (the mean value for the present group was 288  $\mu\text{g}/100 \text{ mg. creatinine}$ , while that found previously was 280  $\mu\text{g}/100 \text{ mg. creatinine}$ ). The mean value obtained when these 12 subjects experienced hyperoxia was 325  $\mu\text{g}/100 \text{ mg. creatinine}$ , but this value does not differ statistically from either of the above values. Changes in urinary corticosteroids lag behind

any that appear in blood (10), the lag time amounting to about 2 hours. Urinary 17-OHCS determinations apparently are not as useful as plasma cortisol determinations in short-term hyperoxia studies. In future studies, posthyperoxia urinary determinations are, therefore, to be used.

Evidence was obtained of hyperoxia-induced sympathoadrenal depression. As shown in table I, norepinephrine excretion, as well as

TABLE I  
*Summary of results*

Urinary variable	Experimental condition		P
	Normoxia	Hyperoxia	
Epinephrine ( $\mu\text{g.}$ )	1.30	0.56	< .001
Norepinephrine ( $\mu\text{g.}$ )	5.16	2.88	< .01
Ratio: NE/E	4.2	5.3	< .001
17-OHCS ( $\mu\text{g.}$ )*	288	325	NS
Urine volume (ml./hr.)	103	60	< .001
Creatinine (mg./hr.)	82	80	NS
Urea (gm.)	1.46	1.33	NS
Uric acid (mg.)	31	32	NS
Potassium (mEq.)	5.4	5.1	NS
Sodium (mEq.)	16.5	11.4	< .01
Phosphate (as mg. P)	40	28	< .01
Ratio: Na/K	3.4	2.6	< .01

Except where otherwise indicated, urinary constituents are expressed as quantity/100 mg. creatinine.

\*n = 12.

epinephrine excretion, was lower during hyperoxia than during normoxia. The reduction in norepinephrine excretion amounted to 44%, while that for epinephrine amounted to 57%. These differences in magnitude of reduction suggest that the two parts of the sympathoadrenal system differ in oxygen-sensitivity. This differential effect is evident in the norepinephrine/epinephrine ratio (NE/E).

It was recognized that mask discomfort would be a factor in both test situations. Other investigators (11) have noted that mask effects may obscure effects of hyperoxia. To test for mask influence, the present results were compared with those obtained previously for nonstressed (nonmasked) subjects. The present

group, when normoxic, had the same mean NE/E ratio as the nonmasked group (for both, the mean NE/E value was 4.2); however, epinephrine and norepinephrine values were relatively high, which suggests that the mask had a stimulatory effect on the sympathoadrenal system. Despite this opposing influence, hyperoxia-induced depression was clearly demonstrated.

Urine volume differences (table I) also seem to represent mask-oxygen interplay. According to Currie and Ullmann (2), breathing through external airway resistances leads to polyuria, not because of differences in tidal or minute volume of ventilation or chemical changes in the blood, but rather because of intrathoracic pressure fluctuations which reflexively depress antidiuretic hormone secretion. The finding of a lower rate of urine flow during hyperoxia suggests that oxygen in excess has a counteracting influence on mask-induced changes. The site at which oxygen acts to reduce urine output remains to be determined. The finding of reduced urine output in association with reduced plasma cortisol concentration and reduced catecholamine excretion is of interest, since impaired excretion of water has been observed following adrenalectomy, and treatment with either corticosteroids or catecholamines improves water excretion in adrenalectomized animals (12).

Despite the variation in urine output, creatinine excretion did not vary significantly (table I). With creatinine variation thus shown to be random in character, all other urinary constituents were expressed as ratios with creatinine. Along with creatinine, insignificant variation was found for potassium, urea, and uric acid (table I). On the basis of these findings, it does not seem that general metabolic status was greatly different on the two test occasions.

Urinary sodium and phosphate differentiated hyperoxia from normoxia (table I). The sodium values, on both occasions, were high in comparison with the previously studied non-stressed subjects who averaged 8.1 mEq. 100

mg. creatinine. This suggests that the oxygen mask was influential on sodium excretion and that hyperoxia was a partially counteracting factor. Of importance is the finding that the mean Na/K ratio following hyperoxia approached that found for nonmasked subjects (who averaged 2.4 mEq. sodium per mEq. potassium). Phosphate excretion during normoxia was high relative to the value found in nonmasked subjects who averaged 30 mg./100 mg. creatinine. In this respect, there also seems to have been interplay between the factors of oxygen pressure and mask discomfort.

#### 4. DISCUSSION

This study, while only preliminary, gave fairly definitive results. Evidence of adrenocortical and sympathoadrenal depression was found, and there was evidence of mask-oxygen interaction. Although the primary interest was on effects of oxygen-breathing, the finding of mask-hyperoxia interplay seems a valuable one, since mask discomfort and preflight hyperoxia are factors in the flying situation as well as in decompression studies. These factors, in combination, undoubtedly have contributed to results obtained in many experimental studies and may have made interpretations difficult. Recently, Marchbanks et al. (9) evaluated adrenocortical, sympathoadrenal, and metabolic aspects in pilots flying single-place, high-performance aircraft and found, by means of these same plasma and urinary determinations, variation not seen in pilots who were off-duty. Comparison of the results for normoxic, mask-wearing subjects in the present experiment with the results for one of the flying groups proved interesting. The flying group averaged 1.82  $\mu$ g. epinephrine, which is only slightly higher than the value obtained in the present mask-breathing, normoxic group (1.30  $\mu$ g.). The same is true for their norepinephrine excretion, the flying group averaging 5.72  $\mu$ g. and the masked group averaging 5.16  $\mu$ g. The mean NE/E ratio for the flying group was 3.2, while that for the masked group was 4.2. Urinary 17-OHCS values for these two groups were also similar, the flying group averaging 298  $\mu$ g. and the masked group

averaging 288  $\mu\text{g}$ . However, the flying group averaged 13.2  $\mu\text{g}$ . of cortisol per 100 ml. plasma, which is significantly above the level noted in the masked group (7.8  $\mu\text{g}./100$  ml. plasma). Mask discomfort, therefore, may have been a contributing factor in the catecholamine response to flight, but it does not account for the plasma cortisol response to flight. The flying group did not show abnormal phosphate excretion, but in sodium excretion they approached the level found for the present masked (normoxic) group, averaging 14.6 mEq./100 mg. creatinine (the masked group averaged 16.5 mEq.). There was further resemblance in that the flying group had a mean Na/K ratio of 3.6 (the masked group averaged 3.4). Mask discomfort, which is one of the many factors in the flying complex, seemingly accounts for a number of the so-called "flight" effects.

Apart from these practical considerations, the finding of evidence of adrenocortical depression is of interest, and it may be interpreted as a compensatory change. Support for this comes from the study of Gerschman et al. (6), who showed (in rodents) that adrenalectomy

tomy led to increased resistance to hyperoxia and that administration of cortisone counteracted the beneficial effect of adrenalectomy. Gerschman and Fenn (7) noted that rats kept in pure oxygen at 1 atmosphere showed no signs of adrenocortical stimulation nor symptoms of oxygen poisoning; with higher oxygen pressures, symptoms of oxygen poisoning appeared and there was evidence of adrenocortical stimulation. It is well established that oxygen effects are roughly proportional to the partial pressure and duration of exposure (11); and it is logical to think that, with oxygen pressure at only 1 atmosphere, adrenocortical depression may account, in part, for the slow onset of symptoms. Since the evidence points toward sympathoadrenal depression as well, it seems that generalized neuroendocrine depression represents an early response to hyperoxia. Individuals vary greatly in their reactions to oxygen, and a given individual may vary greatly on different occasions (11). It may be that neuroendocrine status contributes to this variability. Of some pertinence is the finding of seasonal variation in catecholamine excretion (5, 8). We are, therefore, currently investigating oxygen-sensitivity in relation to season.

#### REFERENCES

- Brown, H., E. Englert, Jr., S. Wallach, and E. L. Simons. Metabolism of free and conjugated 17-hydroxycorticosteroids in normal subjects. *J. Clin. Endocr.* 17:1191-1201 (1957).
- Currie, J. C. M., and E. Ullmann. Polyuria during experimental modifications of breathing. *J. Physiol. (London)* 155:438-455 (1961).
- Daly, W. J., and S. Bondurant. Circulatory effects of oxygen breathing. *Aerospace Med.* 33:333 (1962).
- Feller, R. P. Modification of the trihydroxyimide method for the estimation of epinephrine and norepinephrine in urine. *SAM Report* 60-71, Aug. 1960.
- Feller, R. P., and H. B. Hale. Human sympathoadrenal responsiveness in autumn, winter, and spring. *SAM-TDR-63-46*, June 1963.
- Gerschman, R., D. L. Gilbert, S. W. Nye, P. W. Nadig, and W. O. Fenn. Role of adrenalectomy and adrenal-cortical hormones in oxygen poisoning. *Amer. J. Physiol.* 178:346-350 (1954).
- Gerschman, R., and W. O. Fenn. Ascorbic acid content of adrenal glands of rats in oxygen poisoning. *Amer. J. Physiol.* 176:6-8 (1954).
- Hale, H. B., E. W. Williams, and J. P. Ellis, Jr. Catecholamine excretion in heat-acclimatized men. *SAM-TDR-63-20*, Mar. 1963.
- Marchbanks, V. H., Jr., H. B. Hale, and J. P. Ellis, Jr. Stress responses of pilots flying 6-hour overwater missions in F-100 and F-104 aircraft. *Aerospace Med.* 34:15-18 (1963).
- Migeon, C. J., F. H. Tyler, J. P. Mahoney, A. A. Florentin, H. Castle, E. L. Bliss, and L. T. Samuels. The diurnal variation of plasma levels and urinary excretion of 17-hydroxycorticosteroids in normal subjects, night workers, and blind subjects. *J. Clin. Endocr.* 16:622-633 (1956).
- Mullinax, P. F., Jr., and D. E. Beischer. Oxygen toxicity in aviation medicine. An analysis of recent literature. *J. Aviation Med.* 29:660-667 (1958).

12. Ramey, E. R., and M. S. Goldstein. The adrenal cortex and the sympathetic nervous system. *Physiol. Rev.* 37:155-195 (1957).
13. Reddy, W. J. Modification of the Reddy-Jenkins-Thorn method for estimation of 17-hydroxycorticosteroids in urine. *Metabolism* 3:489-492 (1954).
14. Sweat, M. L. Adrenocorticosteroids in peripheral and adrenal venous blood of man. *J. Clin. Endocr.* 15:1043-1056 (1955).
15. Von Euler, U. S. *Noradrenaline*. Springfield, Ill.: Charles C Thomas, 1956.